

Pediatric Focused Safety Review: Risperdal® (risperidone)

**Pediatric Advisory Committee Meeting
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Food and Drug Administration**

Outline

- Background Drug Information
- Prior Pediatric Study Description and Results
- Pediatric Labeling Changes
- Pre-existing Pediatric Safety Labeling Information
- Drug Use Trends
- Adverse Events (September 2009 – July 2014)
- Summary and Conclusions
- Questions for Committee

Background Drug Information

- **Drug Name (active ingredient):** Risperdal® (risperidone)
- **Original Market Approval:** December 29, 1993
- **Therapeutic Category:** Atypical Antipsychotic
- **Available Dosage Forms:** Oral solution, tablet, and oral disintegrating tablets.
 - Injectable Form (Risperdal Consta) excluded from this review (not approved for use in pediatric patients)
- **Sponsor:** Janssen Pharmaceuticals

Risperdal[®] Drug Information

- **Approved Indications**
 - **Schizophrenia (ages 13 years and older)**
 - **Manic or Mixed Episodes with Bipolar I Disorder**
 - **Monotherapy:** treatment of acute manic or mixed episodes associated with Bipolar I Disorder **(ages 10 years and older)**
 - **Adjunctive therapy** with lithium or valproate treatment of acute manic or mixed episodes associated with Bipolar I Disorder **(adults only)**
 - **Irritability associated with Autistic Disorder (5 years and older)**

Pediatric Efficacy Study and Results

- 6-week, Randomized, Double-Blind, Placebo-Controlled Fixed-Dose (weight-based: high dose and low dose)
- Enrolled 96 patients (ages 5 – 17 years) with irritability and other behavioral disturbances associated with autism (DSM-IV Criteria) to two dose groups (high and low). Approximately 80% patient completion
- Statistically significant improvement for the primary endpoint, Aberrant Behavior Checklist – Irritability (ABC-I) subscale, in the Risperdal high dose group only compared with placebo. ($p < 0.0001$; difference in LS means -7.9 for drug vs -3.5 for placebo)

Pediatric Labeling Changes following Review of Pediatric Study

- **Section 6.1 Clinical Trial Experience: Adverse Reactions**
 - Headache and Pyrexia added to Adverse Reactions Table
 - Section for “Other Adverse Reactions Observed During the Clinical Trial Evaluation of Risperidone” updated to include the terms “neutropenia” and “head titubation”
- **Section 8.4 Pediatric Use**
 - Summary of pediatric results added to labeling
 - Specific language included to reflect efficacy demonstrated in high-dose risperidone group only

Risperdal® (risperidone)

Pre-Existing Pediatric Specific Safety Information in Labeling

Adverse Reactions in Section 8.4 Pediatrics

- **Tardive Dyskinesia** (Warnings and Precautions 5.4)
- **Metabolic Changes**
 - Weight Gain (Warnings and Precautions 5.5; Adverse Reactions 6.1)
 - Hyperglycemia ,Diabetes Mellitus, Dyslipidemia not specifically addressed in 8.4 but addressed in Warnings and Precautions
- **Somnolence** (Adverse Reactions 6.1; 6.2; Dosage and Administration 2.1, 2.2, 2.3)
- **Hyperprolactinemia** (Warnings and Precautions 5.6)
 - Galactorrhea and gynecomastia
- **Growth and Sexual Maturation** (Section 8.4 only)

(Cross references to other relevant sections of labeling are provided in parenthesis.)

Patients dispensed oral risperidone

National estimates of patients, by patient age*, who received prescriptions for oral risperidone dispensed from U.S. outpatient retail pharmacies

August 2013 through July 2014

	Patients (N)	Share (%)
Total patients	1,704,763	100.00%
0 - 16 years	339,886	19.94%
0 - 1 years	105	0.03%
2 - 4 years	7,928	2.33%
5 - 9 years	108,486	31.92%
10 - 12 years	106,835	31.43%
13 - 16 years	148,544	43.70%
17+ years	1,385,879	81.29%
Unknown Age	979	0.06%

*Patient age groups are inclusive of all patients up to the day before their next birthday. For example, patients aged 0 - 16 years includes patients aged 16 years and 11 months.

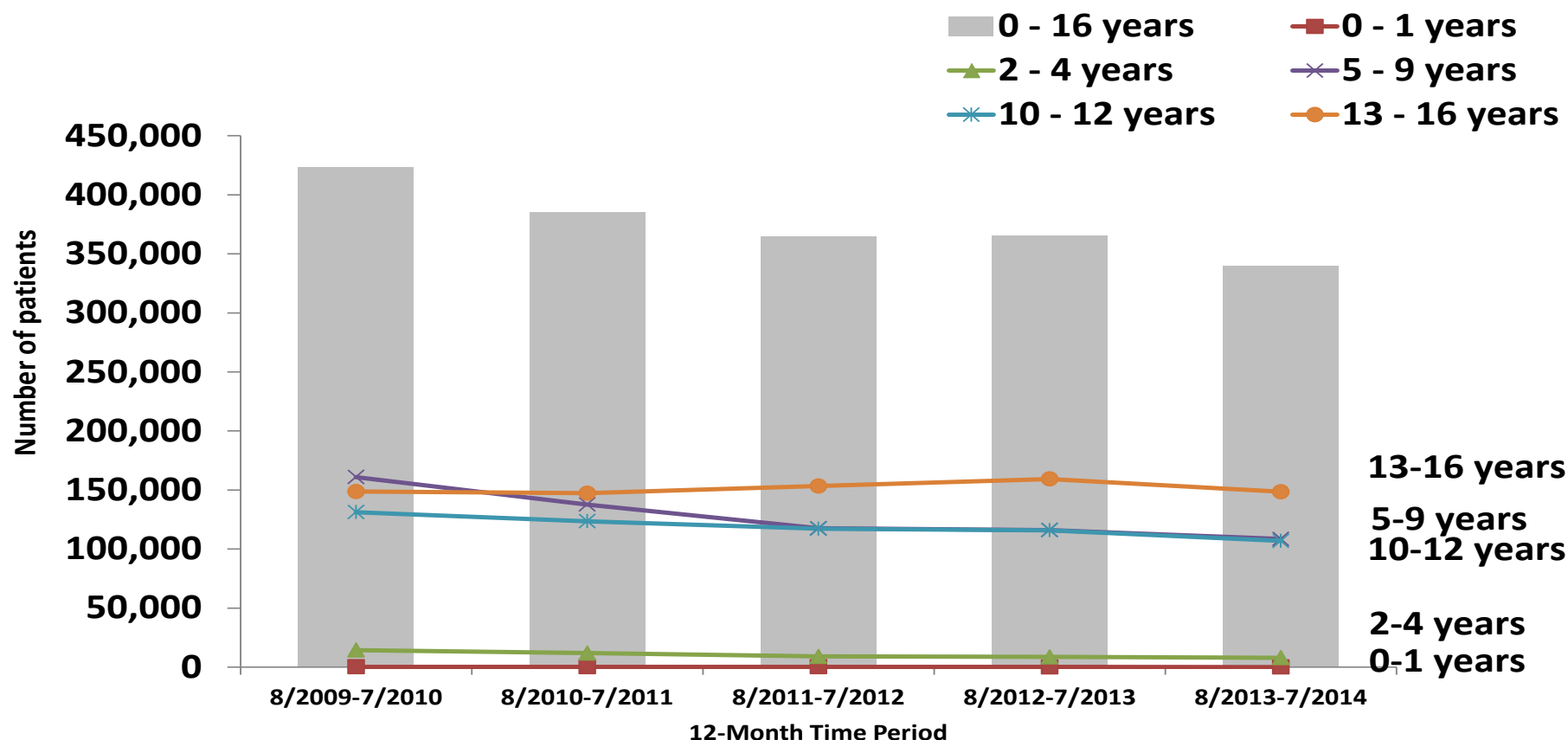
**Summing patients across patient age bands will result in double counting and overestimates of patient counts.

Source: IMS Health, Vector One®: Total Patient Tracker. August 2009 through July 2014. Data extracted November 2014.

Pediatric patients dispensed oral risperidone

August 2009 – July 2014

National estimates of *pediatric patients (0-16 years)*, by patient age, who received prescriptions for oral risperidone dispensed from U.S. outpatient retail pharmacies



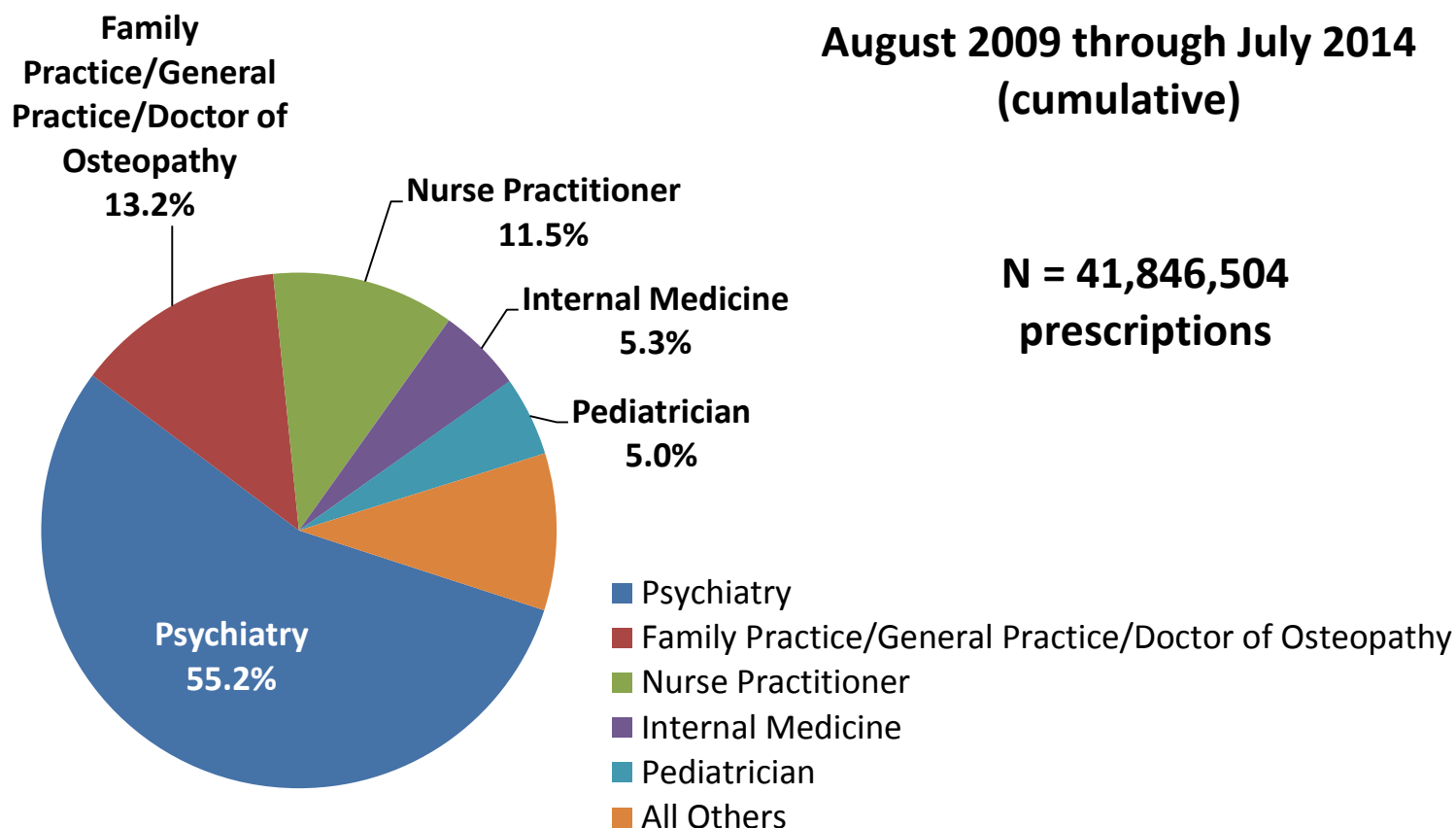
Source: IMS Health, Vector One®: Total Patient Tracker. August 2009 through July 2014. Data extracted November 2014.

Prescriber specialties for oral risperidone

National estimates of total prescriptions dispensed for oral risperidone, stratified by top 5 prescriber specialties, from U.S. outpatient retail pharmacies

August 2009 through July 2014
(cumulative)

N = 41,846,504
prescriptions



Source: IMS Health, National Prescription Audit™. August 2009 through July 2014. Data extracted November 2014.

Pediatric indications for oral risperidone use

August 2009 through July 2014

Top diagnoses associated with the use of oral risperidone in pediatric patients (0-16 years), stratified by patient age, as reported from U.S. office-based physician survey

- 0-1 years*: bipolar affective (ICD-9 296.7)
- 2-4 years*: infantile autism (ICD-9 299.0)
- 5-9 years*: affect psychoses (ICD-9 296.9)
- 10-12 years*: affect psychoses
- 13-16 years*: attention deficit disorder (ICD-9 314.0) and affect psychoses

***Drug use mentions are small for reliable national estimates of use by diagnoses. These mentions indicate that a given drug was mentioned during an office visit, but do not necessarily result in a prescription being generated.**

Prior Advisory Committee Presentations

- **November 18, 2008 Pediatric Advisory Committee**
 - One year post-exclusivity adverse event review for Risperdal® (risperidone)
 - Use of Risperdal® (risperidone) oral formulations in the pediatric and adult populations appeared to be increasing relative to three prior 12-month study periods examined
 - PAC Recommended FDA
 - » Conduct additional evaluations of on and off-label drug use; Follow-up specific safety concerns for atypical antipsychotic use; Assess concomitant drug use; Delay labeling changes
- **June 9 – 10, 2009 Psychopharmacologic Drugs Advisory Committee: Antipsychotics**
 - Conclusion: Significant risks associated with drug class may be monitored and communicated through labeling. FDA may consider differential labeling of drugs and comparative drug trials
- **December 8, 2009 Pediatric Advisory Committee**
 - FDA Office of Pediatric Therapeutics: Clinical Summary of Pediatric Metabolic AERs Reports; FDA Division of Epidemiology/OSE: Drug Use of Atypicals by Pediatric Age Subgroups; NICHD/NIH BPCAQ: Atypical Antipsychotics Working Group
 - Committee concluded that adverse events were adequately labeled

Total Adult and Pediatric FAERS Reports* with Risperidone (September 1, 2009 to July 31, 2014)

	All reports (US)	Serious**(US)	Death (US)
Adults (≥ 17 yrs.) [±] Sept. 1, 2009 – July 31, 2014	7397 (1973)	7098 (1695)	1029 (445)
Pediatrics (0- < 17 yrs.) Sept. 1, 2009 – August 1, 2012 August 2, 2012 – July 31, 2014	635 (251) 380 (106)	591 (212) 361 (88)	39 (34) 7 (2)

*May include duplicates

**Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening events, hospitalization (initial or prolonged), disability, congenital anomaly and other serious important medical events.

[±]Reported from September 1, 2009 – July 31, 2014

[∞] Reported from September 1, 2009 (Date of last AERS search for review of Atypical Antipsychotics) – August 2, 2012 (Approval date of sNDA for pediatric labeling Risperdal)

§Reported from August 2, 2012 (Approval date of sNDA pediatric labeling Risperdal) – July 31, 2014

Selection of Serious Pediatric Cases with Risperidone

**Total serious pediatric reports
reviewed
(N = 400)**

**Reports assessed but excluded from case series
(n=364 Includes 33 deaths)**

- Duplicates (n = 116)
- Does not meet inclusion criteria (n = 202)
- Transplacental exposure, adult patients, long-acting injectable (n = 31)
- Previously presented to PAC in 2008 (n = 15)

**Pediatric serious
cases (n = 36)**

(23 serious unlabeled AEs
13 deaths)

Case Selection: Reviewed Cases Excluded from Case Series n=364, including 33 deaths[±]

- **Does not meet inclusion criteria (n = 202)**
 - Labeled event (n = 104)
 - Confounding concomitant disease or medication (n = 41)
 - Insufficient information to determine causality (n = 37)
 - No temporal relationship (n = 11)
 - Product substitution or quality issue (n = 7)
 - No adverse event reported (n = 2)

[±] Deaths include 17 duplicate cases, 1 in adult case, 15 cases presented at 2008 PAC

Characteristics of Reviewed Serious Pediatric Cases Risperdal® (risperidone) (n=36)

Age (n=36)	1 month - <2 years	1
	2- < 6 years	3
	6- <12 years	13
	12- < 17 years	19
Sex	Male	23
	Female	9
	Unknown	4
Serious Outcome	Death	13
	Hospitalization	12
	Life-threatening	1
	Disability	1
	Other serious	9

Characteristics of Serious Pediatric Cases Risperdal® (risperidone) (n=36)

Country of reporter	United States	n = 12	
	Foreign	n = 24	
Reported Reason for Use	ADHD/Mental retardation	n = 4	“Behavioral problems” n = 1
	Depression	n = 3	Insomnia n = 1
	Bipolar disorder	n = 2	Epilepsy n = 1
	Psychotic disorder	n = 2	“Mood altered” n = 1
	Abnormal behavior	n = 1	Oppositional defiant disorder n = 1
	Aggression	n = 1	Schizophrenia n = 1
	Anxiety	n = 1	Sedation n = 1
	Asperger’s disorder	n = 1	Tourette’s disorder n = 1
	Autism	n = 1	Unspecified n = 12

Summary of Fatal Pediatric Adverse Events

Case Reports with Risperdal® (risperidone) (n=13)

- **Cases with Known/Reported Causes of Death (n = 10)**
 - Suicide/Overdose (n = 3)
 - Cardiac (n = 3)
 - Cerebrovascular (n = 2)
 - Pulmonary (n = 1)
 - Seizure (n = 1)
- **Cases with Unknown/Unreported Causes of Death (n = 3)**

Fatal Pediatric Case Reports (n=13)

Risperdal® (risperidone)

Suicide/Overdose (n = 3)

- 14-year-old (unspecified sex) *completed suicide* by intentional acute oral ingestion of acetaminophen, risperidone, and zolpidem. No additional clinical information reported.
- 14-year-old (unspecified sex) *completed suicide* by intentional acute oral ingestion of olanzapine, risperidone, and fluoxetine.
- 10-year-old male died following acute exposure to: quetiapine, risperidone, clonazepam, lorazepam, alprazolam, valproic acid, atomoxetine, methylphenidate, loratadine, and omeprazole. (Note: medications presented in order of “cause rank.” No other clinical information. Reason for death was “other malicious,” and event reported as “*death due to acute exposure.*”

Note: All cases reported by American Association of Poison Control Centers (AAPCC) Toxic Exposure Surveillance System

Fatal Pediatric Case Reports (n = 13)

Risperdal® (risperidone)

Cardiac (n = 3)

- 15 year old male with epilepsy, aggressive behavior, mood disorder, and impulsiveness died from “cardio-respiratory arrest” approximately 2 months after starting levetiracetam and risperidone. No autopsy performed.
- 10 month old male with extensive thermal burns (77% BSA and airways) died after ventricular tachycardia with torsades de pointes. Treated with 13 medications, including risperidone, voriconazole and ciprofloxacin. History notable for hypokalemia and aspergillosis sepsis.
- 10 year old male with history of pervasive, development disorder treated with multiple medications, including risperidone developed cardiorespiratory arrest within 5 minutes of receiving Japanese Encephalitis vaccine and died hours thereafter from “arrhythmia”.

Fatal Pediatric Case Reports (n=13), continued

Risperdal® (risperidone)

Cerebrovascular (n = 2)

- 11-year-old male with Tourette's disorder hospitalized for hyperosmolar hyperglycemic nonketotic coma and type 2 diabetes 7-8 months after starting risperidone 0.5 mg orally daily and died one week after hospital admission. No concomitant medications. Autopsy concluded "cerebral edema and stroke related to the hyperosmolar hyperglycemic coma as the cause of death."
- 9-year-old patient (unspecified sex) with Attention Deficit Disorder experienced a fatal stroke 12 days after starting risperidone, (dose not specified). No concomitant medications. No report of an autopsy performed.

Fatal Pediatric Case Reports (n = 13), continued

Risperdal® (risperidone)

Pulmonary (n = 1)

- 8-year-old male with autism and asthma taking risperidone and salbutamol experienced an asthma attack. Treated initially with epinephrine, dexamethasone, and levalbuterol in the emergency room (ER). Later the same evening, he had “mucous plug, and respiratory arrest. No autopsy performed

Fatal Pediatric Case Reports (n = 13), continued

Risperdal® (risperidone)

Seizure (n = 1)

- 15-year-old male in foster care with depression and fatigue treated with risperidone oral solution and tablets experienced several seizures... leading to death. No concomitant medications. No past medical history of epilepsy reported. No other details provided.

Fatal Pediatric Case Reports (n = 13), continued

Risperdal® (risperidone)

Unknown Cause of Death (n = 3)

- 8 year old male on risperidone (unknown dose, indication and therapy dates) for “several months” died suddenly “from a natural origin” No concomitant medications reported.
- 8 year old patient (unspecified sex) on chlorpromazine, haloperidol, and risperidone (unspecified dose, indication and therapy dates) experienced an unspecified “adverse reaction and had a fatal outcome.”
- 15-year-old male on risperidone (unspecified dose, indication and therapy dates). Reporter noted that the “drug administered [was] contrary to recommended age.” Unknown if patient was receiving risperidone at time of death. No cause of death or autopsy reported . No medical history and concomitant medications reported.

Cases of Serious Non-Fatal Unlabeled Adverse Events Risperdal® (risperidone) (n=23)

Psychiatric (n = 12)

- **Suicide attempts, suicidal ideations, self-injurious behaviors, or intentional overdose (IOD)** (n = 7)
 - Four cases confounded by other meds (sertraline, lamotrigine, valproate/valpromide)
 - Sertraline: Boxed Warning for suicidality
 - Lamotrigine and Valproate: Warning for suicidal behavior and ideation
 - One case confounded by a history of “anxiodepressive syndrome”
 - One case of intentional risperidone over dose after receiving medication as long-term therapy
 - One case recovered from “suicide attempt, hallucinations” and other adverse events after a dose increase of risperidone and hydroxyzine

(Risperdal is labeled for use in schizophrenia. According to the CDC data, approximately 1/3 of schizophrenics will attempt suicide and eventually about 1 out of 10 will take their own lives.*)

Cases of Serious Non-Fatal Unlabeled Adverse Events Risperdal® (risperidone) (n=23)

Psychiatric (n = 12) continued

- **Aggression** (n = 4)

- Two cases confounded by sertraline or methylphenidate; both labeled for aggression in the Warnings section
- Two cases confounded by histories of mental retardation or hydrocephalus and shunt

(Currently approved labeling contains related term “agitation.”)

- **Paroxysmal perceptual alteration (PPA)** (n = 1)

(The syndrome of PPA is characterized by hypersensitivity of perception, psychedelic experience, and somatic schema disorder. In patients with chronic schizophrenia, attacks occur abruptly, mainly in the evening, and may be precipitated by fatigue. During attacks, patients may also suffer from mood and thought alteration but they are aware that symptoms of PPA are unreal. PPA associated with conventional antipsychotic usage.)

Serious Non-Fatal Unlabeled Adverse Events Risperdal® (continued)

- **Nervous System Disorders (n = 2)**
 - Cerebral embolism and infarct (n = 1)
 - Memory Loss (n = 1)
- **Blood and Lymphatic Disorders:** pancytopenia (n = 1)
- **Cardiac Disorders:** Torsade de Pointes (n = 1)
- **Gastrointestinal/Hepatobiliary Disorders:** hepatic cytolysis, cholestasis (n = 1)
- **Immune System/Skin Disorders:** Toxic Epidermal Necrolysis (n = 1)
- **Other (n=5; one of each):**
 - Nodule
 - Testicular Pain
 - Arthritis
 - Thyroid Function Tests Abnormal
 - Vasculitis

Select Case Reports for Serious Non-Fatal Unlabeled Adverse Events (n=23) Risperdal® (risperidone)

- **Cerebral infarction (n=1)**

- 15-year-old male received risperidone 1-2 mg daily for Asperger's disorder for six years.
- Two years after dose increase of risperidone, he experienced cerebral embolism resulting in cerebral infarction.
- Treated with aspirin/dipyridamole, risperidone discontinued.
- Recovering and in rehabilitation at the time of reporting.

- **Torsade de Pointes (n = 1)**

- 14-year-old female hospitalized for pharyngitis.
- Medications included risperidone 0.5mg ODT every 8 hrs and oral ondansetron 4 mg. Risperidone increased to 1mg every 8 hrs and given concomitantly for 7 days with ondansetron.
- Patient went into cardiac arrest and torsades de pointes for 6 minutes, 4 days after both medications discontinued. Notably patient was recovering in PICU from DRESS due to lamotrigine at time of event.
- The combination of risperidone and ondansetron, or ondansetron alone were suspected as the cause of the event.

Summary Pediatric Focused Safety Review

Risperdal® (risperidone)

- This concludes the pediatric focused safety review.
- No new safety signals were identified.
- FDA recommends to continue routine monitoring of adverse events associated with use of risperidone.
- Does the Committee concur?

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Committee Questions and Discussion